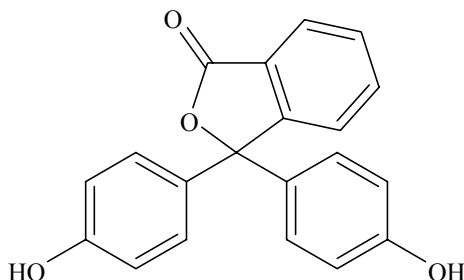


**PHENOLPHTHALEIN**  
**CAS No. 77-09-8**  
First Listed in the *Ninth Report on Carcinogens*



## CARCINOGENICITY

Phenolphthalein is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of increased incidence of malignant and/or combination of malignant and benign tumors in multiple tissue sites and in multiple species. In a two-year B6C3F<sub>1</sub> mouse carcinogenicity study, NTP 465 (1996) concluded that phenolphthalein, administered in feed, induced significant increases in the incidence of histiocytic sarcoma and lymphomas of thymic origin in males and females and malignant lymphoma (all types) and benign ovarian sex cord stromal tumors in females. In the corresponding Fischer 344 rat dietary carcinogenicity study, phenolphthalein induced significant increases in the incidence of benign pheochromocytoma of the adrenal medulla in males and females and renal tubule adenoma in males (NTP 465, 1996). In a 6-month dietary study with female heterozygous p53-deficient transgenic mice, phenolphthalein induced a significant increase in the incidence of malignant lymphoma of thymic origin (Dunnick et al., 1997).

There are no data available to evaluate the carcinogenicity of phenolphthalein in humans.

## ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

The malignant thymic lymphomas induced by phenolphthalein in female heterozygous p53-deficient transgenic mice exhibited a loss of the normal p53 allele, suggesting the involvement of a mutagenic mechanism in tumor induction and/or progression (Dunnick et al., 1997).

Phenolphthalein causes enhanced oxygen radical production in *in vitro* systems. *In vivo*, reduction of phenoxyl radicals could allow reformation of phenolphthalein, establishing a futile cycle of oxidation and reduction, thereby generating more free radical species. Thus, phenolphthalein may be a significant source of oxidative stress in physiological systems.

Although negative for mutagenicity and DNA damage in bacteria, phenolphthalein exhibits genetic activity in several *in vitro* and *in vivo* mammalian assays. Phenolphthalein was positive for the induction of chromosomal aberrations in cultured Chinese hamster ovary cells in the presence of metabolic activation and induced *hprt* gene mutations, chromosomal aberrations, and morphological transformation in Syrian hamster embryo cells. Phenolphthalein was also positive for the induction of micronucleated erythrocytes in mice following multiple but not

single treatments administered by gavage or dosed feed. Phenolphthalein also induced micronuclei in female heterozygous p53-deficient transgenic mice exposed via dosed feed for 26 weeks. Abnormal sperm were induced in male mice but not male rats treated with phenolphthalein via dosed feed for 13 weeks. Phenolphthalein was negative for Na/K ATPase gene mutations and aneuploidy in Syrian hamster embryo cells.

No data are available that would suggest that the mechanisms thought to account for tumor induction by phenolphthalein in experimental animals would not also operate in humans. Phenolphthalein causes oxidative stress and also demonstrates the capability to alter tumor suppressor gene pathways, which are both mechanisms believed to be involved in human cancer.

## **PROPERTIES**

Phenolphthalein is an odorless, white or faintly yellow-white powder comprising minute, triclinic crystals (Budavari, 1996; NTP 465, 1996). It has a melting point of 258-262 °C. It is almost insoluble in water, very slightly soluble in chloroform, and soluble in alcohol, diethyl ether, dilute solutions of alkali hydroxides, and hot solutions of alkali carbonates. Phenolphthalein-titrated solutions are colorless at pH < 8.5 and pink to deep-red at pH > 9 (Budavari, 1996).

## **USE**

Phenolphthalein in 1% alcoholic solution is used as a visual indicator in titrations of mineral and organic acids and most alkalies (Budavari, 1996). It is also used in a variety of ingested products as well as in some scientific applications. Because phenolphthalein is odorless and tasteless, it can be incorporated easily in tablets, powder, and liquid. It has been commonly used as a laxative, available worldwide as an over-the-counter chocolate or gum laxative product. The official dose is 60 mg, but adults usually require 100 to 200 mg (Fingl, 1965). Bedridden patients require 500-mg doses (Sollman, 1957).

## **PRODUCTION**

Currently there is one producer of phenolphthalein in the United States with an annual production of 250 tons (197 metric tons or Mg) (SRIC, 1997a). In 1989, there were two U.S. manufacturers of the compound (HSDB, 1997). The number of manufacturers of phenolphthalein-containing laxatives in 1997 was 20 (U.S. FDA, 1997). Combined sales of the top three phenolphthalein-containing drugs, Correctol<sup>®</sup>, Phillips<sup>®</sup>, and Ex-Lax<sup>®</sup>, totaled 16.4% of the laxative market in 1989 (Drug Store News, 1990), 23.9% in 1992 (Advertising Age, 1993), and 19.9% in the period July 1993-July 2, 1994 (DeNitto, 1994). The three drugs were still among the top-selling laxatives in 1995 (SRIC, 1997b). Ex-Lax<sup>®</sup>, which continued to hold a position in the top three in 1996, accounted for about 7% of the brand-name sales (Suplee, 1997; Drug Topics, 1997). The use of phenolphthalein in laxatives has decreased since the FDA proposed (September of 1997) the reclassification of its use in over-the-counter laxative products (U.S. FDA, 1997). Producers of Correctol<sup>®</sup> and Feen-a-Mint<sup>®</sup> brand products replaced phenolphthalein with bisacodyl in January 1996. Bayer's Phillips' GelCaps was voluntarily removed from the market in mid-1997. Novartis AG, the marketer of Ex-Lax<sup>®</sup>, announced in late August 1997 that its product would be reformulated, substituting senna for phenolphthalein (Suplee, 1997; Drug Topics, 1997).

## EXPOSURE

The major routes of human exposure to phenolphthalein are ingestion, dermal contact, and inhalation of contaminated air originating from process units manufacturing the compound. The general population is exposed to phenolphthalein through its common application as an over-the-counter drug, particularly as a laxative. Many studies show that the use of laxatives to relieve constipation and to maintain regularity in bowel habits is widespread in the United States; however, few studies report on the prevalence of phenolphthalein laxative use.

From studies of four U.S. populations (Harari et al., 1989; Everhart et al., 1989), it would appear that no more than 10% of the U.S. population has used phenolphthalein-containing laxatives as often as once per month, but up to 5% may have used them weekly or more often. In one study of 424 cases of invasive adenocarcinoma of the colon and 414 controls in Washington state, ages 30 to 62 years, it was found that 13.6% of the subjects reported constipation requiring treatment (use of a laxative, enema, or prunes), 4.7% reported ever use of phenolphthalein laxatives, and 3.5% reported use of phenolphthalein laxatives at least 350 times in their lifetimes (Jacobs and White, 1998). In three U.S. populations of 268 to 813 persons comprising approximately equal numbers of cases of adenomatous colorectal polyps and controls, 0.97 to 5.1% of the subjects used phenolphthalein laxatives at least once per week. The two North Carolina groups included subjects aged 30 to 89 years, 58% and 53% of which were female; the group in Los Angeles, California, included subjects aged 50 to 74 years of which 34% were female. Mean ages of the three groups were comparable (59 to 62 years). The frequent phenolphthalein laxative users represented 8 to 30% of all frequent laxative users. The ever use of phenolphthalein laxatives in the two North Carolina groups was 17.5% and 25%, with 10% and 7% using them at least once per month (Longnecker et al., 1997).

Potential occupational exposure could occur through inhalation or dermal contact for workers involved in the manufacturing, formulating, packaging, or administering of drugs containing phenolphthalein. The National Occupational Exposure Survey (NOES), conducted by NIOSH between 1981 to 1983, listed 75,243 workers (26% female) as being potentially exposed to phenolphthalein. The number of Health Services employees potentially exposed to compound was 20,122 (65% female) (NIOSH, 1990).

## REGULATIONS

Phenolphthalein is regulated by EPA under the Clean Air Act (CAA). Emission standards are given for organic hazardous air pollutants for chemical manufacturing process units that produce phenolphthalein. FDA, under the Food, Drug, and Cosmetic Act (FD&CA), regulates phenolphthalein-containing drug products as new drugs. In the *Federal Register* notice, which affects 21 CFR Part 310 and 334, FDA proposed to reclassify phenolphthalein from Category I (generally recognized as safe and effective and not misbranded) to Category II (not generally recognized as safe and effective and misbranded) and added it to a list of non-monograph active ingredients. Phenolphthalein would be added to 21 CFR Section 310.545(a)(12)(iv), the list of stimulant laxatives. The notice concluded with the statement: "The FDA considers use of phenolphthalein a potential risk to humans. These findings of rodent carcinogenicity and genotoxicity in several test systems indicate that chronic use could lead to damage to the human genome (including p53, which is known to be a tumor suppressor gene) and could increase the risk of malignancy." The FDA invited comments on these findings, and in late 1997 was reviewing written comments received from industry (U.S. FDA, 1997). OSHA regulates phenolphthalein under the Hazard Communication Standard. Regulations are summarized in Volume II, Table B-119.